REMARKS

Reconsideration of the rejections set forth in the Office action mailed January 5, 2005 is respectfully requested, for the reasons discussed below. Claims 1-11, 15-17 and 19-27 are currently pending.

I. Amendments

Claim 1 has been amended to unambiguously recite that the probe molecule, whether it is a nucleic acid or nucleic acid analog, is fully charged. Support is found, for example, at page 12, line 23 of the specification.

II. The Invention: Benefits over the Prior Art

As discussed in the Background of the specification (page 1, lines 13-16), different-length highly charged oligomers, such as nucleic acids, are commonly separated in the prior art using charge-based separation methods, such as ion exchange chromatography or electrophoresis. The separation of different-length DNAs or RNAs, which have different charges, in a charge-bearing medium is thus well established, and is not the focus of the present invention.

The present invention, on the other hand, allows the separation of different uncharged (or substantially uncharged) oligomers in a charge-bearing medium. It is the discovery of the applicants, as embodied in independent claim 1, that duplexes of different, substantially uncharged analyte molecules with the same fully charged probe molecule can be separated in a charge-bearing medium, even when all the duplexes are identically charged (as is the case with fully uncharged, or identically charged, analyte molecules).

The working examples illustrate the success of the claimed method in separating uncharged oligomers by ion exchange chromatography. For example, in Example 1 (page 15), each of several uncharged oligomers, varying in length from 13 to 20 subunits, was hybridized with the same probe DNA. The specific probe DNA in this case was a 20-mer complementary to the longest analyte molecule (page 15, lines 20-22). Accordingly, each of the different duplexes had the same charge (-20). As shown in Figs. 5A-B, all the duplex species were resolved.

The method of the invention eliminates the need to use very high or very low (ionizing) pH's to separate such oligomers, as was done in prior art methods of ion exchange separation (page 1, lines 18-20).

III. Rejections under 35 U.S.C. §102(b)

Claims 1-11, 16-17, 19-20, and 23-27 were rejected under 35 U.S.C. §102(b) as being anticipated by Cummins *et al.*, U.S. Patent No. 5,874,213. This rejection is respectfully traversed for the following reasons.

A. The Claims

The invention of independent claim 1 is discussed above.

Claim 1 has been amended to address the Examiner's statement at page 3 of the Office Action (first full paragraph) regarding the language "said specific probe molecule is a nucleic acid or fully charged nucleic analog". Applicants note that a "nucleic acid", in accordance with its accepted meaning, is always fully charged; however, the claim has been amended to recite "a fully charged nucleic acid" to make this feature unambiguous.

B. The Examiner's Position

In characterizing the Cummins reference, the Examiner states that "Cummins et al. clearly discloses a method involving the hybridization of PNA [peptide nucleic acids] to target nucleic acids" (page 3 of Office Action). Similarly, the Examiner states that "the method of Cummins et al. forms a duplex with a highly charged oligomeric compound (DNA or RNA) with uncharged oligomeric compound (PNA)" (page 4 of Office Action, first paragraph). The Examiner further states that "In sum, both methods [that of the applicants and the reference] involve the production of duplex, wherein said duplex is formed between a naturally occurring charged nucleic acid and an uncharged (synthesized) oligomer (i.e., PNA) and therefore, for the above reasons, Cummins *et al.* anticipate the invention as claimed" (page 4 of Office Action).

The statements above address a method of forming a duplex between a charged oligomeric species and an uncharged oligomeric species. However, this is not what is claimed. The rejection does not even address the final step of the applicants' method; i.e., "*separating said duplexes from each other* and from single stranded species within the medium".

C. The Cited Reference

Cummins *et al.*, in fact, teaches neither the first step nor the second step of independent claim 1. The first step of the claimed method comprises "applying to a charge-bearing

separation medium a mixture of (i) the different analyte molecules and (ii) the specific probe molecule", where "the analyte molecules are composed of linked subunits of which at least 90% are uncharged, and the specific probe molecule is a nucleic acid or a fully charged nucleic acid analog". In the second step, the duplexes are separated from each other.

In Cummins, on the other hand, the only duplexes that are separated from each other are duplexes of each of two or three different-length DNAs (which are fully charged) with a single PNA (which is substantially uncharged, having a single lysine residue). Accordingly, these procedures employ a plurality of different charged molecules (the DNAs) and a single, uncharged (or substantially uncharged) molecule (PNA).

In the Office Action, the Examiner does not appear to fully take into account the roles and characteristics of "probe" and "analyte" molecules as recited in the claims, and appears to consider these terms to be merely semantic, or even interchangeable. For example, the Examiner asserts that the "analyte molecules" employed by Cummins are peptide nucleic acids (page 3 of Office Action, last paragraph). However, if this were the case, in order to anticipate applicants' claim 1, the reference would have to show at least the step of:

"(a) applying to a charge-bearing separation medium a mixture of (i) the different analyte molecules [i.e., a population of different peptide nucleic acid molecules] and (ii) the specific probe molecule" [i.e. a specific fully charged oligomer, in accordance with the claims].

This step is not shown in the reference. As stated above, the applicants can find no instance in Cummins in which a population of different, uncharged (or substantially uncharged) molecules (such as PNA's), in combination with a specific, fully charged molecule (such as DNA), are applied to a charge-bearing medium.

Since the reference does not disclose all of the elements set out above in claim 1, and its dependent claims, the claims cannot be anticipated by this reference under 35 U.S.C. §102(b). In view of this, the applicant respectfully requests the Examiner to withdraw the rejection under 35 U.S.C. §102(b).

IV. Rejections under 35 U.S.C. §103(a)

Claim 15, which recites an ion exchange separation medium, was rejected under 35 U.S.C.

§103(a) as being obvious over Cummins *et al.*, U.S. Patent No. 5,874,213, discussed above, in view of Ness *et al.*, U.S. Patent No. 6,613,508, which discloses ion exchange chromatography as one method of size-based separation of nucleic acids from other molecules (column 4, lines 10-15 and 21).

Claims 21-22, which recite morpholino oligomers, were rejected under 35 U.S.C. §103(a) as being obvious over Cummins *et al.*, U.S. Patent No. 5,874,213, discussed above, in view of Valdivia et al. (WO 96/36734), which notes that PNA and morpholino compounds have certain advantages over nucleic acid probes.

These rejections are respectfully traversed for the following reasons.

For the reasons described above, Cummins, the primary reference, teaches neither step 1 nor step 2 of the applicants' claimed method. The applicants contend that the claimed method would not have been obvious over the teachings of Cummins, taken alone or in combination with the secondary references.

Again, the Examiner does not appear to fully take into account the roles and characteristics of "probe" and "analyte" molecules as recited in the claims. The Examiner appears to take the position that the difference between the "probe" and "analyte" molecules in the applicants' claims is merely semantic: "While Cummins et al. terms this [a highly charged oligomer or nucleic acid] as target nucleic acids while Applicants terms it as "probe" is irrelevant, for the characteristics of both are the same" (page 3 of Office Action).

The applicants do not agree that the difference between the role of fully charged oligomers in the method of Cummins, and in the claimed method, is "irrelevant". In Cummins, a plurality of different nucleic acids (fully charged oligomers) is hybridized with the same probe molecule (e.g. a labeled PNA). In this case, the duplexes are differently charged, deriving their different charges from the analyte (nucleic acid) molecules.

For example, in Example 3 of Cummins, the three duplexes (18-, 19-, and 20-mers of DNA, each hybridized with a lysine-terminated 20-mer PNA) have net charges of -17, -18 and -19 (as illustrated below). The duplexes are separated by CGE on the basis of their different charges, and the hybridized labeled PNA's assist in detection.

Duplexes separated in Cummins *et al.*, Example 3:

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DNA ------------------    ------------------    --------------------
PNA oooooooooooooooooo+   oooooooooooooooooo+   oooooooooooooooooo+

      charge = -17            charge = -18            charge = -19
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However, Cummins does not teach or suggest, for example, the separation of duplexes of 18-mer, 19-mer, and 20-mer PNA's with the same 20-mer DNA molecule (where the duplexes would be identically charged, as in the hypothetical illustration below). Such a separation, not the separations actually shown in Cummins, would be encompassed by the applicants' invention.

Separation not shown or suggested in Cummins *et al.*:

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DNA --------------------   --------------------   --------------------
PNA ooooooooooooooooo+     ooooooooooooooooo+     ooooooooooooooooo+

      charge = -19            charge = -19            charge = -19
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The applicants contend that, on the basis of the rather unsurprising disclosure (by Cummins *et al.*) that differently charged species can be separated in a charged medium, it would not have been obvious to one skilled in the art that identically charged species could be separated in a charged medium (e.g., electrophoretically or by ion exchange), as shown by the applicants.

The secondary references are cited for their brief discussions of morpholino oligomers and ion exchange chromatography, respectively, and add nothing to the teachings of Cummins that is pertinent to independent claim 1. It is of no consequence, for example, that Ness teaches different forms of charge-based separation, since neither Ness nor Cummins suggests the applicants' claimed method using any form of separation. Therefore, even if the teachings of each reference were combined with Cummins, the references in combination would not teach or suggest the claimed invention.

In view of the foregoing, the applicants respectfully request the Examiner to withdraw the rejections under 35 U.S.C. §103(a).

V. Conclusion

In view of the foregoing, the applicant submits that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4403.

Respectfully submitted,

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